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LETTER TO THE EDITOR

Persistent endotheliopathy in the pathogenesis of long COVID syndrome: Comment from von Meijenfeldt et al.

To the Editor

With great interest we read the recent brief report by Dr. Fogarty and colleagues providing evidence for persistent endothelial cell activation in convalescent COVID-19 patients.[1] The authors showed that plasma levels of von Willebrand factor (VWF), factor VIII (FVIII), and soluble thrombomodulin were elevated at a median of 68 days after initial COVID-19 symptom resolution or discharge from the hospital. Interestingly, not all these patients experienced severe disease. Levels of endothelial injury markers were associated with long-term symptoms, including dyspnoea, fatigue, and concentration impairment, often referred to as long COVID. The authors intriguingly suggest that endothelial injury contributes to the pathogenesis of this syndrome. In accordance with Fogarty et al. we have previously shown sustained hemostatic alterations in plasma of patients 4 months after hospital admission with COVID-19 infection.[2] Here, we would like to share follow-up data from this cohort at 8 and 12 months after initial COVID-19, and associate the hemostatic status at these time points with functional impairment post–COVID-19 to assess whether hemostatic changes may indeed be linked to long COVID. We included 44 patients from the COMMUNITY (COVID-19 Immunity) study who were admitted to Danderyd Hospital, Stockholm, Sweden, with COVID-19 between April and June 2020, as described previously.[3] Blood samples were drawn on admission and at 4, 8, and 12 months after hospital discharge. We performed various assays to assess the hemostatic status of these patients, including plasma levels of hemostatic proteins, a thrombin generation assay, and a functional assay of fibrinolysis. These methods and other specifics of this cohort have been described elsewhere.[3] We compared the hemostatic status of patients at 8- and 12-month follow-up with that on admission, and at the 4-month follow-up (the latter have been published previously[2]). We included previously described reference values of the various tests performed established in 29 healthy controls. To assess functional impairment post–COVID-19, the Sheehan Disability Scale was used, and determined by questionnaires at the 8- and 12-month follow-ups. Participants were asked to score the impact of their symptoms on work life, social life, and family life. Functional impairment was scored as follows; 0: none, 1–3: mild, 4–6: moderate, 7–10: marked. All participants gave informed consent and the study was approved by the Stockholm Ethical Review Board.

Table 1 displays the hemostatic status of COVID-19 patients on admission and 4, 8, and 12 months after hospital discharge. D-dimer levels that are known to be markedly elevated during COVID-19 infection declined to comparably low levels at 4-, 8-, and 12-month follow-up, although levels remained numerically higher than in healthy controls. VWF and FVIII also decreased over time and were comparable to levels in healthy controls 12 months after hospital discharge. Plasminogen activator inhibitor type 1 (PAI-1) levels were substantially elevated on admission and at 4 months after discharge,[3] and, despite a gradual decline, remained significantly elevated both 8 and 12 months after hospital discharge compared to levels found in healthy controls, which may be related to obesity, which is known to be associated with elevated PAI-1 levels.[4] In addition, clot lysis time, which is determined in part by PAI-1 plasma levels, remained significantly prolonged at 8- and 12-month follow-ups compared to healthy controls. Thrombin generation potential was still elevated at 8 months post–hospital discharge, but was comparable to healthy controls at 12 months. Interestingly, a recent study using rotational thromboelastometry to assess clot formation and fibrinolysis showed normalization of these parameters at 6 months after discharge of the intensive care for COVID-19.[5]

Next, we assessed functional impairment of convalescent COVID-19 patients 8 and 12 months after hospital discharge. Notably, approximately 15% of patients reported marked impairment of their functioning 1 year after initial COVID-19. Overall, the impact of complaints on the three aspects of life decreased over time (Wilcoxon signed ranked test, median [interquartile range (IQR)] Sheehan score 8 vs. 12 months; work life 5 [0–5] vs. 2 [0–5] $P = .007$, social life 3 [0–5] vs. 3 [0–6] $P = .071$, family life 2 [0–6] vs. 2 [0–5] $P = .011$). Hemostatic markers at 8 and 12 months were not associated with severity of post-COVID complaints in any of the domains of life. In addition, we compared hemostatic markers between patients with none or mild complaints with patients with moderate to marked complaints at 8 and 12 months post–hospital discharge, and found no difference in hemostatic markers between these two groups in any of the domains of life (Table S1 in supporting information).

In conclusion, our results suggest that endothelial cell activation and plasma hypercoagulability assessed with thrombin generation assays persist up to 8 months after hospital discharge, and normalize after 1 year. A hyperfibrinolytic state persists at 12 months, but this may be related to obesity. In this study, hemostatic markers were not associated with functional impairment scored by patients,

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TABLE 1 Hemostasis tests in COVID-19 patients on admission and at 4-month, 8-month, and 12-month follow-up compared to healthy controls

	Healthy controls ($n = 29$)	COVID-19 patients on admission ($n = 44$)	COVID-19 patients 4-month follow-up ($n = 44$)	COVID-19 patients 8-month follow-up ($n = 44$)	COVID-19 patients 12-month follow-up ($n = 44$)	*P*-value Healthy controls vs. 8-month/1-year follow-up
Standard hemostasis tests						
D-dimer (ng/mL)	290 [205–445]	1110 [640–1910][a,b,c]	390 [313–510]	420 [258–555]	360 [295–605]	.03/.04
Additional hemostasis tests						
Factor VIII (%)	136 [114–157]	218 [162–282][a,b,c]	159 [132–196][e]	151 [123–187]	149 [125–181]	.03/.06
VWF (%)	108 [83–128]	348 [248–413][a,b,c]	120 [86–153]	118 [88–152]	100 [82–142]	.27/.97
PAI-1 (ng/mL)	0.60 [0.10–0.75]	2.60 [1.83–4.78][b]	2.80 [0.70–4.90][d]	1.08 [0.52–2.61]	1.54 [0.77–2.63]	<.01/<.001
Thrombin generation assay						
ETP (nM IIa*min)	606 [422–773]	796 [586–932][c]	855 [699–980][e]	760 [625–852][f]	623 [469–718]	<.01/.69
Peak (nM IIa)	167 [123–215]	215 [169–267]	243 [196–279][e]	242 [201–269][f]	192 [153–230]	<.001/.11
Lag time (min)	2.00 [1.67–2.00]	2.65 [2.00–3.00][a,b,c]	2.00 [1.67–2.33][d,e]	2.00 [1.67–2.00]	2.00 [1.67–2.00]	.59/.48
Velocity index (nM IIa/min)	77 [62–112]	97 [67–123][a,b]	134 [94–161][e]	139 [117–154][f]	100 [80–131]	<.001/.03
Clot lysis time (min)	66 [62–70]	82 [70–91]	77 [67–85]	77 [69–89]	74 [67–91]	<.001/<.01

Note: The results are presented as median [interquartile range]. Comparisons between patients on admission and follow-up were made using repeated measures analysis of variance. Comparisons with healthy controls were made with the use of the Mann-Whitney *U* test. A *P*-value <.05 was considered statistically significant.

Abbreviations: ETP, endogenous thrombin potential; PAI-1, plasminogen activator inhibitor type 1; VWF, von Willebrand factor.

[a]Significant difference between admission vs. 4-month follow-up.

[b]Significant difference between admission vs. 8-month follow-up.

[c]Significant difference between admission vs. 12-month follow-up.

[d]Significant difference between 4-month vs. 8-month follow-up.

[e]Significant difference between 4-month vs. 12-month follow-up.

[f]Significant difference between 8-month vs. 12-month follow-up.

which contrasts with the data from Fogarty and colleagues, which were scored at a median of 68 days after symptom resolution or hospital discharge. We determined functional impairment scores at 8 and 12 months after initial disease. Functional impairment scores at 4 months were not available in our cohort, nor did we perform a 6-min walking test as described by Fogarty et al. We concur that ongoing endothelial cell activation and hypercoagulability may contribute to long COVID, although our data indicate that larger and more detailed investigations into factors that contribute to long COVID are warranted.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Conception and design: FM, CT, TL; patient inclusion: SH, CT; data acquisition: SH, CT; laboratory analyses: JA; analysis: FM, TL; interpretation: FM, SH, JA, CT, TL; supervision: CT, TL; drafting of manuscript: FM, TL; revision of the manuscript: SH, CT.

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SUPPORTING INFORMATION

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